PA .NT COOPERATION TREAT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing: 29 October 1998 (29.10.98)	
International application No.: PCT/GB98/01144	Applicant's or agent's file reference: SJK/BP5697164
International filing date: 20 April 1998 (20.04.98)	Priority date: 22 April 1997 (22.04.97)
Applicant: LANE, David, Philip	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

17 September 1998 (17.09.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

Claims:

1. Use of an agent having the property of disrupting the binding of p53 and mdm2 or inhibiting the production of mdm2 in a population of cells, in the preparation of a medicament for activating p53, wherein the population of cells do not overexpress mdm2.

2. The use of claim 1 wherein the p53 is activated for DNA specific binding and transcription.

3. The use of claim 1 or claim 2 wherein the agent comprises a peptide having an amino acid sequence corresponding to human p53 which has the property of binding to mdm2.

4. The use of claim 3 wherein the peptide is less than 25 amino acids in length and has an amino acid sequence having at least 70% amino acid sequence identity with a corresponding portion of human p53.

5. The use of claim 3 or claim 4 wherein the agent includes the peptide motif FxxxW, where x is any amino acid.

6. The use of claim 1 or claim 2 wherein the agent has the property of binding to one or more regions of mdm2 involved in binding to p53.

7. The use of claim 6 wherein the agent is an antibody which is capable of blocking a p53 binding site of mdm2.

8. The use of claim 1 or claim 2 wherein the agent has the property of competing with mdm2 for binding p53, but does not inhibit a biological activity of p53.

9. The use of claim 8 wherein the agent is an antibody

capable of blocking a mdm2 binding site of p53.

10. The use of claim 1 or claim 2 wherein the agent is an antisense oligonucleotide capable of inhibiting the synthesis of mdm2 in the population of cells.

11. The use of any one of the preceding claims wherein the medicament is for the treatment of cancer, a viral condition or other condition associated with non functional p53 or mdm2.

12. A method of activating p53 comprising exposing a population of cells to an agent having the property of disrupting the binding of p53 and mdm2 or inhibiting the production of mdm2 so that p53 in the cells is activated, wherein the cells do not overexpress mdm2.

13. The method of claim 12 wherein the p53 is activated for DNA specific binding and transcription.

14. The method of claim 12 or claim 13 wherein the agent comprises a peptide having an amino acid sequence corresponding to human p53 which has the property of binding to mdm2.

15. The method of claim 12 or claim 13 wherein the peptide is less than 25 amino acids in length and has an amino acid sequence having at least 70% amino acid sequence identity with a corresponding portion of human p53.

16. The method of any one of claims 12 to 15 wherein the agent includes the peptide motif FxxxW, where x is any amino acid.

17. The method of claim 12 or claim 13 wherein the agent has the property of binding to one or more regions of mdm2 involved in binding to p53.

18. The method of claim 17 wherein the agent is an antibody which is capable of blocking a p53 binding site of mdm2.

19. The method of claim 12 or claim 13 wherein the agent has the property of competing with mdm2 for binding p53, but does not inhibit a biological activity of p53.

20. The method of claim 19 wherein the agent is an antibody capable of blocking a mdm2 binding site of p53.

21. The method of claim 12 or claim 13 wherein the agent is an antisense oligonucleotide capable of inhibiting the synthesis of mdm2 in the population of cells.

22. A cell line that does not overexpress mdm2, the cell line being transfected with a reporter construct comprising nucleic acid encoding a reporter polypeptide under the control of promoter elements capable of responding to p53 activated for DNA specific binding to direct expression of the reporter polypeptide.

23. A method of screening test substances for the property of disrupting the binding of p53 and mdm2 or inhibiting the production of mdm2, the method comprising employing cells which do not overexpress mdm2, the cells being transfected with a reporter construct comprising nucleic acid encoding a reporter polypeptide under the control of promoter elements that respond to the level of p53 activated for DNA specific binding to direct expression of the reporter polypeptide, the method comprising exposing the cells to the candidate substances and detecting the presence of the reporter polypeptide.

24. The method of claim 23 wherein test substances are peptides and the cells are transfected an expression vector comprising nucleic acid encoding the peptides so that the

peptide is expressed in the cells.

25. The method of claim 23 or claim 24 wherein the test substances are expressed as fusion with a peptide capable of displaying the test peptide in a particular conformation.

26. The method of claim 25 wherein the peptides are expressed as fusion with thoriedoxin.

27. The method of claim 23 wherein the test substances are microinjected into the cells

28. The method of claim 23 wherein the test substances are coupled to transport molecules so that test substances are transported into the cells.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT" International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* SJK/BP5697164

Box No. I TITLE OF INVENTION MATERIALS AND METHODS RELATING TO INHIBITING THE INTERACTION OF p53 and mdm2

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box i Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

UNIVERSITY OF DUNDEE
DUNDEE
DD1 4HN
GB

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(i.e. country) of nationality:* GB

State *(i.e. country) of residence:* GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box i Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

LANE David Philip
Magicwell House
Balmullo
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KY16 O8N
GB

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(if this check-box is marked, do not fill in below.)*

State *(i.e. country) of nationality:* GB

State *(i.e. country) of residence:* GB

This person is applicant for the purposes of: ☐ all designated ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SIMON KIDDLE and others
MEWBURN ELLIS
YORK HOUSE
23 KINGSWAY
LONDON WC2B 6HP
GB

Telephone No. 0117 9266411

Facsimile No. 0171 240 9339

Teleprinter No. 22762 PATENT G

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

DESIGNATION OF STATE

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked):*

Regional Patent

- [X] **AP** — **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] **EA** — **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkemenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] **EP** — **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] **OA** — **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection desired, specify on dotted line):*

- [X] **AL** Albania
- [X] **AM** Armenia
- [X] **AT** Austria
- [X] **AU** Australia
- [X] **AZ** Azerbaijan
- [X] **BA** Bosnia & Herzegovina
- [X] **BB** Barbados
- [X] **BG** Bulgaria
- [X] **BR** Brazil
- [X] **BY** Belarus
- [X] **CA** Canada
- [X] **CH and LI** Switzerland and Liechtenstein
- [X] **CN** China
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- [X] **CZ** Czech Republic
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- [X] **GH** Ghana
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- [X] **HU** Hungary
- [X] **ID** Indonesia
- [X] **IL** Israel
- [X] **IS** Iceland
- [X] **JP** Japan
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- [X] **KP** Democratic People's Republic of Korea
- [X] **KR** Republic of Korea
- [X] **KZ** Kazakstan
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- [X] **LK** Sri Lanka
- [X] **LR** Liberia
- [X] **LS** Lesotho
- [X] **LT** Lithuania
- [X] **LU** Luxembourg
- [X] **LV** Latvia
- [X] **MD** Republic of Moldova
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- [X] **MK** The former Yugoslav Republic of Macedonia
- [X] **MN** Mongolia
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- [X] **MX** Mexico
- [X] **NO** Norway
- [X] **NZ** New Zealand
- [X] **PL** Poland
- [X] **PT** Portugal
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- [X] **SK** Slovakia
- [X] **SL** Sierra Leone
- [X] **TJ** Tajikistan
- [X] **TM** Turkmenistan
- [X] **TR** Turkey
- [X] **TT** Trinidad and Tobago
- [X] **UA** Ukraine
- [X] **UG** Uganda
- [X] **US** United States of America
- [X] **UZ** Uzbekistan
- [X] **VN** Viet Nam
- [X] **YU** Yugoslavia
- [X] **ZW** Zimbabwe

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- [X] ~~**CY Cyprus**~~
- [X] All and any further PCT States not listed on this form
- [X]

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet need not be included in the request.*

Use this Box in the following cases:

1. If, in any of the Boxes, the space is insufficient to furnish all the information:	*In such case, write "Continuation of Box No. ..." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient;*
in particular:	
(i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available:	*in such case, write "Continuation of Box III" and indicate for each additional person the same type of information as required in Box No. III;*
(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked:	*in such cases write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*
(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America:	*in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*
(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents:	*in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*
(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "Continuation" or "Continuation-in-part":	*in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*
(vi) if there are more than three earlier applications whose priority is claimed:	*in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*
2. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty:	*in such case, write "Statement Concerning Non-Prejudicial Disclosures or Exceptions to Lack of Novelty" and furnish that statement below.*

Continuation of Box IV

ARMITAGE, IAN M.
BRASNETT, ADRIAN H.
BREWSTER, ANDREA R.
CALDERBANK, T. ROGER
COLEIRO, RAYMOND
FORD, MICHAEL F.
GURA, H. ALAN
HACKNEY, NIGEL J.
HAMILTON, ALISTAIR
HARRISON, DAVID C.
KIDDLE, SIMON J.
KREMER, SIMON M.
LINN, S. JONATHAN
LYONS, JUNE, M.
NICHOLLS, KATHRYN M.
O'BRIEN, CAROLINE J.
PAGET, HUGH C.E.
SANDERSON, MICHAEL J.
STONER, G. PATRICK
STUART, IAN
WALTON, SEÁN M.

Continuation of Box No. ?

Box No. VI PRIORITY CLAIM Further priority claims a[illegible]cated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

	Country *(in which, or for which the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of filing *(only for regional or international application)*
item (1)	UK	22 April 1997	9708092.3	
item (2)				
item (3)				

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): 1

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA/

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by*

Country (or regional Office): Day *(day/month/year)*: Number:

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	:	4	sheets
2. description	:	38	sheets
3. claims	:	4	sheets
4. abstract	:	1	sheets
5. drawings	:	4	sheets
Total	**:**	**51**	**sheets**

This international application is accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☒ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☐ priority document(s) *identified in Box No. VI as item(s):*
5. ☒ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. ☒ other *(specify):* 23/77

Figure No. 1 of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request)

.....
SIMON KIDDLE (Appointed Agent)

For receiving Office use only

1. Date of actual receipt of the purported international application:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: **ISA/**
6. ☐ Transmittal of search copy delayed until search fee is paid

2. Drawings:
☐ received:
☐ not received:

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: SJK/BP5697164

Applicant: UNIVERSITY OF DUNDEE

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE ..... £55 [T]

2. SEARCH FEE ..... £780 [S]

International search to be carried out by _____
(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 51 sheets.

first 30 sheets ..... £285 [b_1]

21 remaining sheets x £6 additional amount = £126 [b_2]

Add amounts entered at b_1 and b_2 and enter total at B.... £411 [B]

Designation Fees

The international application contains 71 designations.

11 number of designation fees payable *(maximum 11)* x £65 amount of designation fee = £715 [D]

Add amounts entered at B and D and enter total at I ..... £1126 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT ..... £22 [P]

5. TOTAL FEES PAYABLE
Add amounts entered at T, S, I and P, and enter total in the TOTAL box

£1983
TOTAL

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

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- ☐ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.
- ☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

Deposit Account Number _____ Day *(day/month/year)* _____ Signature _____

Patent

DESIGNATION OF STATES

ARIPO Patent: **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe and any other State which is a Contracting State of the Harare Protocol and of the PCT

[X] **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH** and **LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden and any other State which is a Contracting State of the European Patent Convention and of the PCT

[X] **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **ML** Mali, **MR** Mauritania, **Ne** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT

[X] **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakstan, **MD** Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan and any other state which is a member state of EAPC and a Contracting State of the PCT

National Patent

[X] **AL** Albania
[X] **AM** Armenia
[X] **AT** Austria
[X] **AU** Australia
[X] **AZ** Azerbaijan
[X] **BA** Bosnia & Herzegovina
[X] **BB** Barbados
[X] **BG** Bulgaria
[X] **BR** Brazil
[X] **BY** Belarus
[X] **CA** Canada
[X] **CH** and **LI** Switzerland & Liechtenstein
[X] **CN** China
[X] **CU** Cuba
[ ]
[X] **CZ** Czech Republic
[X] **DE** Germany
[X] **DK** Denmark
[X] **EE** Estonia
[X] **ES** Spain
[X] **FI** Finland
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[X] **GE** Georgia
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[X] **ID** Indonesia
[X] **IL** Israel
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[X] **JP** Japan
[X] **KE** Kenya
[X] **KG** Kyrgyzstan
[X] **KP** Democratic People's Republic of Korea
[X] **KR** Republic of Korea
[X] **KZ** Kazakstan
[X] **LC** Saint Lucia
[X] **LK** Sri Lanka
[X] **LR** Liberia
[X] **LS** Lesotho
[X] **LT** Lithuania
[X] **LU** Luxembourg
[X] **LV** Latvia
[X] **MD** Republic of Moldova
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[X] **MK** Macedonia
[X] **MN** Mongolia
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[X] **SL** Sierra Leone
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Check-boxes reserved for States which have become party to the PCT after issuance of this sheet

[ ] .....

[ ] .....

Note: this sheet lists all states known to be PCT Contracting States at the 1 April 1998

Mewburn Ellis, April 1998
3designx.frm

[redacted]ENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
SJK/BP5697164		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 98/ 01144	20/04/1998	22/04/1997
Applicant		
UNIVERSITY OF DUNDEE et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

   - [ ] filed with the international application.
   - [X] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**

   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. 1

   - [X] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/GB 98/01144

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 12-21 partially, insofar as they concern in vivo methods, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

[redacted]tional Application No
[redacted]/GB 98/01144

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/17 C12N5/10 G01N33/50 C07K16/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 20238 A (UNIV JOHNS HOPKINS) 14 October 1993 cited in the application see page 7, paragraph 5 see page 10, paragraph 3 - page 12, paragraph 1 ---	1-11
X	WO 96 02642 A (UNIV DUNDEE ;PICKSLEY STEVEN MICHAEL (GB); LANE DAVID PHILIP (GB)) 1 February 1996 cited in the application see page 1, paragraph 1 see page 3, paragraph 2 - page 6, paragraph 2 --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 August 1998	01/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sitch, W

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	BLAYDES ET AL: "TOLERANCE OF HIGH LEVELS OF WILD-TYPE P53 IN TRANSFORMED EPITHELIAL CELLS DEPENDENT ON AUTO-REGULATION BY MDM-2" ONCOGENE, vol. 14, no. 15, 17 April 1997, pages 1859-1868, XP002075048 cited in the application see page 1859 see abstract see page 1866, paragraph 3 ---	1-11
X	BÖTTGER ET AL: "IDENTIFICATION OF NOVEL MDM2 BINDING PEPTIDES BY PHAGE DISPLAY" ONCOGENE, vol. 13, 1996, pages 2141-2147, XP002075049 cited in the application see the whole document ---	1-11
A	DATABASE MEDLINE FILE SERVER STN KARLSRUHE ABSTRACT 93390942, KOVAR ET AL: "NARROW SPECTRUM OF INFREQUENT P53 MUTATIONS AND ABSENCE OF MDM2 AMPLIFICATION IN EWING TUMOURS" XP002075050 see abstract & ONCOGENE, vol. 8, no. 10, October 1993, pages 2683-2690, ---	
P,X	WO 98 01467 A (CIBA GEIGY AG ;CANCER RES CAMPAIGN TECH (GB); LANE DAVID (GB); BOE) 15 January 1998 see the whole document see page 11, paragraph 4 - paragraph 5 see page 16, paragraph 2 - page 17, paragraph 1 -----	1-28

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/01144

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9320238 A	14-10-1993	US 5411860 A	02-05-1995
		AT 159985 T	15-11-1997
		AU 681851 B	11-09-1997
		AU 4278893 A	08-11-1993
		CA 2133306 A	14-10-1993
		DE 69315068 D	11-12-1997
		DE 69315068 T	09-04-1998
		DK 635068 T	20-04-1998
		EP 0635068 A	25-01-1995
		ES 2110608 T	16-02-1998
		JP 7505294 T	15-06-1995
		US 5420263 A	30-05-1995
		US 5550023 A	27-08-1996
		US 5519118 A	21-05-1996
		US 5618921 A	08-04-1997
		US 5756455 A	26-05-1998
		US 5708136 A	13-01-1998
		US 5736338 A	07-04-1998
		US 5606044 A	25-02-1997
		US 5702903 A	30-12-1997
WO 9602642 A	01-02-1996	US 5702908 A	30-12-1997
		US 5770377 A	23-06-1998
		AU 684194 B	04-12-1997
		AU 2987695 A	16-02-1996
		CA 2195533 A	01-02-1996
		EP 0773996 A	21-05-1997
		JP 10506525 T	30-06-1998
WO 9801467 A	15-01-1998	AU 3847997 A	02-02-1998

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
KIDDLE, Simon
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

Date of mailing (day/month/year) 29 October 1998 (29.10.98)	
Applicant's or agent's file reference SJK/BP5697164	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/GB98/01144	20 April 1998 (20.04.98)	22 April 1997 (22.04.97)

Applicant
UNIVERSITY OF DUNDEE et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,BR,CA,CN,EP,IL,JP,KP,KR,NO,PL,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AL,AM,AP,AT,AZ,BA,BB,BG,BY,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GE,GH,GM,GW,HU,ID,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NZ,OA,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   29 October 1998 (29.10.98) under No. WO 98/47525

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:
KIDDLE, Simon
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

Date of mailing (day/month/year) 29 October 1998 (29.10.98)	
Applicant's or agent's file reference SJK/BP5697164	**IMPORTANT INFORMATION**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/GB98/01144	20 April 1998 (20.04.98)	22 April 1997 (22.04.97)

Applicant
UNIVERSITY OF DUNDEE et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,SD,SZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,BR,CA,CN,CZ,DE,GB,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US,
   VN

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,ML,MR,NE,SN,TD,TG
   National :AL,AM,AT,AZ,BA,BB,BY,CH,CU,DK,EE,ES,FI,GE,GH,GM,GW,HU,ID,IS,KE,
   KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI,SL,TJ,TM,TR,TT,UA,
   UG,UZ,YU,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent including, where applicable, ES which cannot be elected since it is not bound by Chapter II.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
J. Zahra

Telephone No. (41-22) 338.83.38

Continuation of Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year)	IMPORTANT NOTICE
29 October 1998 (29.10.98)	
Applicant's or agent's file reference	**International application No.**
SJK/BP5697164	PCT/GB98/01144

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

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PATENT COOPERATION TREATY

REC'D 30 JUL 1999
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SJK/BP5697164		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/01144	20/04/1998	22/04/1997
International Patent Classification (IPC) or national classification and IPC A61K38/17		
Applicant UNIVERSITY OF DUNDEE et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17/09/1998	28.07.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Brück, M Telephone No. (+49-89) 2399 8735

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/01144

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-38	as originally filed

Claims, No.:

1-27	as received on	26/05/1999	with letter of	24/05/1999

Drawings, sheets:

1/4-4/4	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-8, 10-19, 21, 22
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-27
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1-27* cf item V, 4.

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section V:

1. Reference is made to the following documents:

   D1 = WO 93/20238

   D2 = WO 96/02642

   D3 = Oncogene, 1997, Vol.14, pages 1859-1868

   D4 = Oncogene, 1996, Vol. 13, pages 2141-2147

2. The present application does not meet the requirements of Article 33(2) PCT, because the subject matter of claims 1-8, 10-19, and 21 does not appear to be novel vis-à-vis documents D1, D2, D3, or D4.

2.1 The independent claims relate to either the second/ further medical use form (claim 1 - cf. item VIII, 2) or a method (claim 12) for the use of an agent (cf. item VIII, 1) for activating p53.

However, the use of an agent which disrupts the binding of p53 and mdm2 or inhibits the production of mdm2 and, therefore, activates p53 has already been disclosed in documents D1 (pages 4-5 and in claim 27) and D2 (abstract, claim 1).
Also, documents D3 (page 1866) and D4 (abstract) suggest the treatment of tumors with molecules that disrupt the p53-mdm-2 interaction.
Therefore, claims 1 and 12 are not novel vis-a-vis documents D1, D2, D3, or D4.
The expression in claims 1 and 12 "wherein the population of cells do not overexpress mdm2", in its present form, characterizes neither the agent nor the condition to be treated and, therefore, cannot confer novelty upon these claims.

2.2 The dependent claims specify the agent
- claims 2 and 13, cf. item VIII, 3
- claims 3 and 14: agent comprises a peptide having an amino acid sequence corresponding (cf. item VIII, 4) to human p53 (D2: page 1, paragraph 1; D4: abstract and page 2142)
- claims 4 and 15: the peptide is shorter than 25 amino acids and has at least 70% amino acid identity with the human p53 (D2: page 1, paragraph 1; D4: abstract and page 2142)
- claims 5 and 16: peptide has the motif FxxxW (D2: page 1, paragraph 1; D3: page 2142)
- claims 6 and 17, cf. item VIII, 5
- claims 7 and 18: an antibody, capable of blocking a p53 binding site of mdm2 (D1: page 10; D3: abstract)
- claims 8 and 19, cf. item VIII, 6
- claims 10 and 21: an oligonucleotide capable of inhibiting the synthesis of mdm2 in the population of the cells (cf. item VIII, 7) (D1: page 10)
- and claim 11 specifies the disease to be treated to be a cancer, viral condition or other condition associated with non-functional p53 or mdm2 (D1: claim 27, D2: abstract, D3: 1866, and D4: abstract).

However, these features have already been disclosed as indicated in parentheses and, therefore, dependent claims 2-8, 10, 11, 13-19, and 21 are not novel vis-a-vis documents D1 or D2.

3. The present application does not meet the requirements of Article 33(3) PCT, because the subject matter of claims 9, 20, and 23-27 does not appear to involve an inventive step vis-à-vis documents D1, D3, or D4.

3.1 Independent claim 22 relates to a screening test for agents that disrupt the p53-mdm2 binding or production of mdm2 by exposing cells to candidate substances and detecting the presence of the reporter polypeptide (cf. item VIII, 8).
The dependent claims specify that the test substances are peptides (claim 24), that the test substances are expressed as fusion with a peptide capable of displaying the test peptide in a "particular conformation" (cf. item VIII, 9-claim 25-

D4: page 2146), that peptides are expressed as fusion with thoriedoxin (claim 26--D4: page 2146), that test substances are microinjected into the cells (claim 27--D3: page 1867), and that test substances are coupled to transport molecules.

The prior art D1-D4 describes agents as suitable anti-cancer drugs which inhibit the mdm2-p53 interaction and, therefore, increase the p53 activity.
The cell lines have already been disclosed in D1 on page 20 in example 6, and in D3 on page 1866, paragraph "DNA transfection", and 1860, paragraph "Selection of clones stably expressing a p53-dependent reporter construct", also describing FRTL-5 cell lines which express mdm-2 mRNA below the limit of detection.

To the skilled man faced with the technical problem--the provision of a screening test--it would have been obvious to use the cell lines in D1 or D3 to screen for suitable compounds and, and therefore, claim 23 does not appear to be inventive.

3.2 Dependent claims 9, 20, and 24-27 appear to contain only additional technical features which are common in the art and are also, therefore, not regarded as inventive.

4. For the assessment of the present claims 1-27 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims.
The EPO does not, for example, recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but may allow claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment, if the claims relate to "the use of X for the manufacture of a medicament for the treatment of the disease Y or conditions associated with Y" (cf. item VIII, 2).

Section VI

1. The portions of the intermediate document (WO 98/01467 priority: 5.7.1996 and 7.4.1997, filing: 4.7.1997, publication: 15.1.1998) interfering with the novelty of the application have no basis in the priority documents, and the document would not, therefore, provide the basis for a novelty objection.

Section VIII:

The application does not fulfill the requirements of Article 6, because the following claims are unclear:

1. The agent in claims 1 and 12 is not clearly defined because the only characterization relates to a result to be achieved, viz., "having the property of disrupting the binding of p53 and mdm2 or inhibiting the production of mdm2 in a population of cells" (cf. PCT Preliminary Examination Guidelines, C-III, 4.7).

2. Claim 1 is formulated in the second/further medical use form but does not relate to any treatment, which renders the claim unclear.
   To render the claim formally clear, it could be formulated as follows: "Use of an agent ... in the manufacture of a medicament for the treatment of tumors associated with a low p53 activity and a low expression of mdm2."
   The difference from the EPO decision T19/86 is that two different patient groups, "sero-negative" and "sero-positive" piglets, are clearly defined.

3. The p53 in dependent claims 2 and 13 is characterized only by a result to be achieved--"wherein p53 is activated for DNA specific binding and transcription"--which renders the claims unclear (cf. PCT Preliminary Examination Guidelines, C-III, 4.7).

4. The expression "corresponding" in claims 3 and 14 does not clearly define the amino acid sequence of the peptide and, therefore, renders the claims unclear.

5. The agent in dependent claims 6 and 17 is characterized only by a result to be achieved--"the property of binding to one or more regions of mdm2 involved in binding to p53"--which renders the claims unclear (cf. PCT Preliminary Examination Guidelines, C-III, 4.7).

6. The agent in dependent claims 8 and 19 is characterized only by a result to be achieved--"the property of competing with mdm2 for binding p53, bur does not inhibit a biological activity of p53"--which renders the claims unclear (cf. PCT Preliminary Examination Guidelines, C-III, 4.7).

7. The antisense oligonucleotide in dependent claims 9 and 21 is characterized only by a result to be achieved--"being capable of inhibiting the synthesis of mdm2 in the population of the cells"--which renders the claims unclear (cf. PCT Preliminary Examination Guidelines, C-III, 4.7).)

8. Claim 22 is unclear, because the claimed cell line is not unambiguously defined; "that does not overexpress mdm2" is an inherent parameter which appears to apply to all 'normal' cells, and the promotor elements are characterized only by a result to be achieved--"being capable of responding to p53 activated for DNA specific binding to direct expression of the reporter polypeptide"--which renders the claims unclear (cf. PCT Preliminary Examination Guidelines, C-III, 4.7).

9. The expression "particular conformation" in claim 24 does not characterize the peptide unambiguously and, therefore, renders the claim unclear.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

KIDDLE, Simon
MEWBURN ELLIS
York House
23 Kingsway
London WC2B 6HP
GRANDE BRETAGNE

RECEIVED
30 JUL 1999

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	28.07.99
Applicant's or agent's file reference SJK/BP5697164	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/01144	20/04/1998	22/04/1997

Applicant
UNIVERSITY OF DUNDEE et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	THORNTON, J Tel.(+49-89) 2399-8072

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SJK/BP5697164		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/01144	20/04/1998	22/04/1997
International Patent Classification (IPC) or national classification and IPC A61K38/17		
Applicant UNIVERSITY OF DUNDEE et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17/09/1998	28.07.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Brück, M Telephone No. (+49-89) 2399 8735

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/01144

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-38	as originally filed			

Claims, No.:

1-27	as received on	26/05/1999	with letter of	24/05/1999

Drawings, sheets:

1/4-4/4	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-8, 10-19, 21, 22
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-27
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1-27* cf item V, 4.

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section V:

1. Reference is made to the following documents:

   D1 = WO 93/20238

   D2 = WO 96/02642

   D3 = Oncogene, 1997, Vol.14, pages 1859-1868

   D4 = Oncogene, 1996, Vol. 13, pages 2141-2147

2. The present application does not meet the requirements of Article 33(2) PCT, because the subject matter of claims 1-8, 10-19, and 21 does not appear to be novel vis-à-vis documents D1, D2, D3, or D4.

2.1 The independent claims relate to either the second/ further medical use form (claim 1 - cf. item VIII, 2) or a method (claim 12) for the use of an agent (cf. item VIII, 1) for activating p53.

However, the use of an agent which disrupts the binding of p53 and mdm2 or inhibits the production of mdm2 and, therefore, activates p53 has already been disclosed in documents D1 (pages 4-5 and in claim 27) and D2 (abstract, claim 1).
Also, documents D3 (page 1866) and D4 (abstract) suggest the treatment of tumors with molecules that disrupt the p53-mdm-2 interaction.
Therefore, claims 1 and 12 are not novel vis-a-vis documents D1, D2, D3, or D4.
The expression in claims 1 and 12 "wherein the population of cells do not overexpress mdm2", in its present form, characterizes neither the agent nor the condition to be treated and, therefore, cannot confer novelty upon these claims.

2.2 The dependent claims specify the agent
- claims 2 and 13, cf. item VIII, 3
- claims 3 and 14: agent comprises a peptide having an amino acid sequence corresponding (cf. item VIII, 4) to human p53 (D2: page 1, paragraph 1; D4: abstract and page 2142)
- claims 4 and 15: the peptide is shorter than 25 amino acids and has at least 70% amino acid identity with the human p53 (D2: page 1, paragraph 1; D4: abstract and page 2142)
- claims 5 and 16: peptide has the motif FxxxW (D2: page 1, paragraph 1; D3: page 2142)
- claims 6 and 17, cf. item VIII, 5
- claims 7 and 18: an antibody, capable of blocking a p53 binding site of mdm2 (D1: page 10; D3: abstract)
- claims 8 and 19, cf. item VIII, 6
- claims 10 and 21: an oligonucleotide capable of inhibiting the synthesis of mdm2 in the population of the cells (cf. item VIII, 7) (D1: page 10)
- and claim 11 specifies the disease to be treated to be a cancer, viral condition or other condition associated with non-functional p53 or mdm2 (D1: claim 27, D2: abstract, D3: 1866, and D4: abstract).

However, these features have already been disclosed as indicated in parentheses and, therefore, dependent claims 2-8, 10, 11, 13-19, and 21 are not novel vis-a-vis documents D1 or D2.

3. The present application does not meet the requirements of Article 33(3) PCT, because the subject matter of claims 9, 20, and 23-27 does not appear to involve an inventive step vis-à-vis documents D1, D3, or D4.

3.1 Independent claim 22 relates to a screening test for agents that disrupt the p53-mdm2 binding or production of mdm2 by exposing cells to candidate substances and detecting the presence of the reporter polypeptide (cf. item VIII, 8).
The dependent claims specify that the test substances are peptides (claim 24), that the test substances are expressed as fusion with a peptide capable of displaying the test peptide in a "particular conformation" (cf. item VIII, 9-claim 25-

D4: page 2146), that peptides are expressed as fusion with thoriedoxin (claim 26--D4: page 2146), that test substances are microinjected into the cells (claim 27--D3: page 1867), and that test substances are coupled to transport molecules.

The prior art D1-D4 describes agents as suitable anti-cancer drugs which inhibit the mdm2-p53 interaction and, therefore, increase the p53 activity.
The cell lines have already been disclosed in D1 on page 20 in example 6, and in D3 on page 1866, paragraph "DNA transfection", and 1860, paragraph "Selection of clones stably expressing a p53-dependent reporter construct", also describing FRTL-5 cell lines which express mdm-2 mRNA below the limit of detection.

To the skilled man faced with the technical problem--the provision of a screening test--it would have been obvious to use the cell lines in D1 or D3 to screen for suitable compounds and, and therefore, claim 23 does not appear to be inventive.

3.2 Dependent claims 9, 20, and 24-27 appear to contain only additional technical features which are common in the art and are also, therefore, not regarded as inventive.

4. For the assessment of the present claims 1-27 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims.
The EPO does not, for example, recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but may allow claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment, if the claims relate to "the use of X for the manufacture of a medicament for the treatment of the disease Y or conditions associated with Y" (cf. item VIII, 2).

Section VI

1. The portions of the intermediate document (WO 98/01467 priority: 5.7.1996 and 7.4.1997, filing: 4.7.1997, publication: 15.1.1998) interfering with the novelty of the application have no basis in the priority documents, and the document would not, therefore, provide the basis for a novelty objection.

Section VIII:

The application does not fulfill the requirements of Article 6, because the following claims are unclear:

1. The agent in claims 1 and 12 is not clearly defined because the only characterization relates to a result to be achieved, viz., "having the property of disrupting the binding of p53 and mdm2 or inhibiting the production of mdm2 in a population of cells" (cf. PCT Preliminary Examination Guidelines, C-III, 4.7).

2. Claim 1 is formulated in the second/further medical use form but does not relate to any treatment, which renders the claim unclear.
   To render the claim formally clear, it could be formulated as follows: "Use of an agent ... in the manufacture of a medicament for the treatment of tumors associated with a low p53 activity and a low expression of mdm2."
   The difference from the EPO decision T19/86 is that two different patient groups, "sero-negative" and "sero-positive" piglets, are clearly defined.

3. The p53 in dependent claims 2 and 13 is characterized only by a result to be achieved--"wherein p53 is activated for DNA specific binding and transcription"--which renders the claims unclear (cf. PCT Preliminary Examination Guidelines, C-III, 4.7).

4. The expression "corresponding" in claims 3 and 14 does not clearly define the amino acid sequence of the peptide and, therefore, renders the claims unclear.

5. The agent in dependent claims 6 and 17 is characterized only by a result to be achieved--"the property of binding to one or more regions of mdm2 involved in binding to p53"--which renders the claims unclear (cf. PCT Preliminary Examination Guidelines, C-III, 4.7).

6. The agent in dependent claims 8 and 19 is characterized only by a result to be achieved--"the property of competing with mdm2 for binding p53, bur does not inhibit a biological activity of p53"--which renders the claims unclear (cf. PCT Preliminary Examination Guidelines, C-III, 4.7).

7. The antisense oligonucleotide in dependent claims 9 and 21 is characterized only by a result to be achieved--"being capable of inhibiting the synthesis of mdm2 in the population of the cells"--which renders the claims unclear (cf. PCT Preliminary Examination Guidelines, C-III, 4.7).)

8. Claim 22 is unclear, because the claimed cell line is not unambiguously defined; "that does not overexpress mdm2" is an inherent parameter which appears to apply to all 'normal' cells, and the promotor elements are characterized only by a result to be achieved--"being capable of responding to p53 activated for DNA specific binding to direct expression of the reporter polypeptide"--which renders the claims unclear (cf. PCT Preliminary Examination Guidelines, C-III, 4.7).

9. The expression "particular conformation" in claim 24 does not characterize the peptide unambiguously and, therefore, renders the claim unclear.

Claims:

1. Use of an agent having the property of disrupting the binding of p53 and mdm2 or inhibiting the production of mdm2 in a population of cells, in the preparation of a medicament for activating p53, wherein the population of cells do not overexpress mdm2.

2. The use of claim 1 wherein the p53 is activated for DNA specific binding and transcription.

3. The use of claim 1 or claim 2 wherein the agent comprises a peptide having an amino acid sequence corresponding to human p53 which has the property of binding to mdm2.

4. The use of claim 3 wherein the peptide is less than 25 amino acids in length and has an amino acid sequence having at least 70% amino acid sequence identity with a corresponding portion of human p53.

5. The use of claim 3 or claim 4 wherein the agent includes the peptide motif FxxxW, where x is any amino acid.

6. The use of claim 1 or claim 2 wherein the agent has the property of binding to one or more regions of mdm2 involved in binding to p53.

7. The use of claim 6 wherein the agent is an antibody which is capable of blocking a p53 binding site of mdm2.

8. The use of claim 1 or claim 2 wherein the agent has the property of competing with mdm2 for binding p53, but does not inhibit a biological activity of p53.

9. The use of claim 8 wherein the agent is an antibody capable of blocking a mdm2 binding site of p53.

10. The use of claim 1 or claim 2 wherein the agent is an antisense oligonucleotide capable of inhibiting the synthesis of mdm2 in the population of cells.

11. The use of any one of the preceding claims wherein the medicament is for the treatment of cancer, a viral condition or other condition associated with non functional p53 or mdm2.

12. A method of activating p53 comprising exposing a population of cells to an agent having the property of disrupting the binding of p53 and mdm2 or inhibiting the production of mdm2 so that p53 in the cells is activated, wherein the cells do not overexpress mdm2.

13. The method of claim 12 wherein the p53 is activated for DNA specific binding and transcription.

14. The method of claim 12 or claim 13 wherein the agent comprises a peptide having an amino acid sequence corresponding to human p53 which has the property of binding to mdm2.

15. The method of claim 12 or claim 13 wherein the

peptide is less than 25 amino acids in length and has an amino acid sequence having at least 70% amino acid sequence identity with a corresponding portion of human p53.

16. The method of any one of claims 12 to 15 wherein the agent includes the peptide motif FxxxW, where x is any amino acid.

17. The method of claim 12 or claim 13 wherein the agent has the property of binding to one or more regions of mdm2 involved in binding to p53.

18. The method of claim 17 wherein the agent is an antibody which is capable of blocking a p53 binding site of mdm2.

19. The method of claim 12 or claim 13 wherein the agent has the property of competing with mdm2 for binding p53, but does not inhibit a biological activity of p53.

20. The method of claim 19 wherein the agent is an antibody capable of blocking a mdm2 binding site of p53.

21. The method of claim 12 or claim 13 wherein the agent is an antisense oligonucleotide capable of inhibiting the synthesis of mdm2 in the population of cells.

22. A method of screening test substances for the property of disrupting the binding of p53 and mdm2 or inhibiting the production of mdm2, the method comprising

employing cells which do not overexpress mdm2, the cells being transfected with a reporter construct comprising nucleic acid encoding a reporter polypeptide under the control of promoter elements that respond to the level of p53 activated for DNA specific binding to direct expression of the reporter polypeptide, the method comprising exposing the cells to the candidate substances and detecting the presence of the reporter polypeptide.

23. The method of claim 22 wherein test substances are peptides and the cells are transfected with an expression vector comprising nucleic acid encoding the peptides so that the peptide is expressed in the cells.

24. The method of claim 22 or claim 23 wherein the test substances are expressed as fusion with a peptide capable of displaying the test peptide in a particular conformation.

25. The method of claim 24 wherein the peptides are expressed as fusion with thioredoxin.

26. The method of claim 22 wherein the test substances are microinjected into the cells

27. The method of claim 22 wherein the test substances are coupled to transport molecules so that test substances are transported into the cells.